Editorial

Management of unstable angina: what role intervention, ask the RITA-3 trialists?

Unstable angina usually results from the rupture of an atheromatous plaque within the coronary circulation, which provides a stimulus for platelet deposition and thrombosis.[1] If the thrombus is subocclusive it produces intense regional ischaemia, expressed clinically as unstable angina, and there is an ill defined risk of progression to thrombotic coronary occlusion and myocardial infarction. Chest pain is inevitable and treatment with opiates should not be delayed. Nitrates and β blockers are usually sufficient to correct myocardial ischaemia but dihydropyridine calcium antagonists (nifedipine, amlodipine) should be avoided, particularly in patients who are not taking β blockers.[2]

Because unstable angina is a thrombotic syndrome, treatment with antithrombotic drugs can reduce the risk of myocardial infarction and death. Thrombolytic therapy is unhelpful[3] but three randomised trials have confirmed the benefits of aspirin for improving early prognosis.[4–6] In one trial, unfractionated heparin was shown to have a similar beneficial effect, although there was no clear advantage over aspirin alone.[6] Three further studies have confirmed that the combination of unfractionated heparin and aspirin confers little additional protection to that provided by aspirin alone.[7–9] Nevertheless, meta-analysis has suggested that unfractionated heparin may make a small independent contribution to risk reduction in unstable angina (risk ratio 0.67, 95% confidence interval 0.44 to 1.02), and perhaps for this reason it remains widely used in combination with aspirin.[10]

A range of newer antithrombotic drugs has recently become available. Low molecular weight heparin, which has a more predictable anticoagulant effect than unfractionated heparin and can be given by subcutaneous injection without the need for anticoagulant monitoring, has been the subject of three large randomised trials in unstable angina.[11–13] In two of them dalteparin and aspirin showed no clear benefit over aspirin alone[11] or aspirin in combination with unfractionated heparin.[12] In the third trial, enoxaparin in combination with aspirin resulted in a slightly lower combined incidence of death, myocardial infarction, and recurrent angina than occurred with unfractionated heparin and aspirin.[13] It can be deduced, therefore, that low molecular weight heparin plus aspirin is at least as effective as unfractionated heparin plus aspirin in unstable angina, although there is no compelling evidence of added clinical benefit. It is likely that these comparative studies have overestimated the clinical value of unfractionated heparin, as proper anticoagulant monitoring (regular measurement of partial thromboplastin time with adjustment of infusion rate), which has been written into the study protocols, is rarely adhered to in clinical practice. Moreover, there is now evidence that the use of low molecular weight heparin may be associated with lower administration costs and a significant reduction in resource utilisation, particularly diagnostic cardiac catheterisation and angioplasty.[14 15] For these reasons, the argument for low molecular weight heparin in unstable angina is gaining momentum and it has already replaced unfractionated heparin in many coronary care units.

Potentially more interesting than low molecular weight heparin are drugs that inhibit platelet aggregation by antagonising the glycoprotein IIb/IIIa receptor on the platelet surface membrane. Only abciximab by intravenous infusion is currently available (ReoPro; Eli Lilly) and its value for protecting against major ischaemic events in high risk coronary angioplasty—a category that includes patients with unstable angina—is well established.[16 17] However, abciximab cannot be recommended for the routine management of unstable angina, although there is optimism that orally active IIb/IIIa receptor antagonists soon to become available may provide a useful addition to existing treatments. The recently licensed clopidogrel, which also interferes with platelet aggregation by inhibiting the binding of ADP to its platelet receptor, is being evaluated in unstable angina. Ticlopidine, its more toxic predecessor, has already been shown to be effective, but adverse side effects, particularly the risk of neutropenia, have limited its clinical application[18] Clopidogrel has a safety profile equivalent to that of aspirin but appears to be more effective in protecting against ischaemic events in patients with atherosclerotic vascular disease.[19] There is optimism therefore that it will find a useful role in the management of unstable angina.

Although the medical management of unstable angina is directed towards relieving pain and protecting against myocardial infarction and death, these aims cannot always be achieved. At least 13% of patients remain unstable after hospital admission with ongoing ischaemic chest pain.[20] Moreover, in a review of 10 representative series with a total of nearly 2000 patients, the pooled one year mortality rate was estimated as 10% with a combined infarct and mortality rate of 21%.[21] Whether invasive management strategies involving coronary angiography and revascularisation provide the key to reducing event rates in unstable angina is an important question that remains unanswered. In many units, invasive management is reserved almost exclusively for patients with uncontrolled chest pain who cannot be discharged from hospital. Although these patients do appear to be at heightened risk, the policy is largely pragmatic and there is no clear evidence that it protects against future events. The ECG remains the best predictor of high risk. In a recent study, 14% of patients with ST depression on admission died or had a myocardial infarction within the 30 day follow up period.[22] Risk stratification based on biochemical markers of myocardial injury has been the subject of recent investigation. Thus, increased serum concentrations of troponin T and I (structural proteins found only in cardiac myocytes) occur in about a third of patients with unstable angina and identify a group in whom morbidity and mortality are increased.[23 24] At present, there are no data regarding the value of invasive management in this high risk group.

In the absence of data to support a selective policy of invasive management in high risk patients, it is important to consider whether reductions in event rates might be achieved by a non-selective policy of invasive management applied to all patients with unstable angina. Generally, randomised trials in patients with acute coronary syndromes have been

unable to demonstrate any clear advantage for invasive compared with conservative management strategies.[3 25–27] However, only one of these trials recruited patients with unstable angina, and its clinical relevance is limited because a high crossover rate ensured that the proportion of patients undergoing revascularisation in the conservative group was almost as high as in the invasive group (49% *v* 61%), compromising the trial's ability to discriminate between the two strategies.[3] The more recent report of non-randomised registry data in "organisation to assess strategies for ischemic syndromes" (OASIS) found that higher rates of invasive investigation and revascularisation were associated with a better symptomatic outcome but an increased rate of stroke, and did not appear to influence prognosis in terms of myocardial infarction and death.[28]

Continuing uncertainty about the role of cardiac catheterisation and revascularisation in the management of unstable angina largely accounts for the variations in clinical practice that exist between countries and individual physicians, some of whom recommend an invasive strategy for every case while others restrict it to the minority of patients with uncontrolled chest pain who cannot be discharged from hospital.[28] There is no doubt that the use of invasive management in patients with unstable angina is increasing and using an increasing proportion of health care resources. It is therefore of considerable clinical and social importance to establish whether the invasive management of these patients influences clinical outcome.[29] To answer this question the "randomised intervention treatment of angina" (RITA) trialists have embarked on a large multicentre study in the UK in which conservative and interventional treatment strategies are being compared in patients with unstable angina. In two previous landmark studies, the RITA trialists compared angioplasty with surgical[30] and medical[31] management of coronary artery disease. This, their third study, is no less important and deserves the support of all physicians involved in managing patients with unstable angina.

S KENNON
A TIMMIS

Department of Cardiology Royal Hospitals NHS Trust, London Chest Hospital, Bonner Road, London E2 9JX, UK
email: adam@timmis-lch.demon.co.uk

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